for treating said type I diabetes of glutamic acid decarboxylase and a pharmaceutically acceptable carrier or diluent in an inhaler or nebulizer.

Cancel claims 59, 61-62 and 64-65 without prejudice or disclaimer.

REMARKS

Reconsideration of this application is respectfully requested. By the present amendment, claims 39, 45, 47, 55, 59, 61-62, and 64-65 have been canceled. Claims 37 and 48 have been amended to conform to now canceled claim 65 and, in addition, to require that the claimed treatment be suppression of an autoimmune response associated with the autoimmune disease being treated. These steps were taken strictly to simplify the issues and without adverse inference or admission.

Support for the Present Amendment

Support of the language in claims 37 and 48 which was not present in canceled claim 65 can be found in the working embodiments of the original disclosure as well as in the general description, for example as follows:

> Autoimmune diseases are characterized by an abnormal immune response directed against normal autologous (self) tissues. **[Page 2, lines 11-13]**
>
> "Autoimmune disease" is defined herein as a malfunction of the immune system of mammals, including humans, in which the immune system fails to distinguish between foreign substances within the mammal and/or autologous tissues or substances and, as a result, treats autologous tissues and substances as if they were foreign and mounts an immune response against them. **[P. 9, lines 16-22]**
>
> Autoantigens are antigens normally found within and specific for an

organ or tissue under autoimmune attack which are themselves the primary target of autoimmune response. **[Page 3, lines 19-21]**

"Autoantigen" is any substance or a portion thereof normally found within a mammal that, in an abnormal situation, is no longer recognized as part of the mammal itself by the lymphocytes or antibodies of that mammal, and is therefore the primary target of attack by the immunoregulatory system as though it were a foreign substance. The term also includes antigenic substances which induce conditions having the characteristics of an autoimmune disease when administered to mammals. **[P. 9, lines 23-28]**

[O]ral administration of a bystander antigen can stave off tissue damage done by cells specific for another antigen or antigen fragment. **[Page 5, lines 22-25]**

a "bystander" ... upon ingestion or inhalation [it] suppresses autoimmune response [P. 9, lines 1-3]

spontaneous or induced disease state that presents with specific inflammation of the same organ or tissue as that afflicted in the autoimmune disease. **[P. 10, lines 24-26]**

...cells and cytokines involved **in autoimmune response and its suppression [Page 28, lines 15-16]**

downregulation of cellular inflammatory immune response [P. 47, line 20]

to **suppress the T-cells contributing to said response [Original claims 1,15 and 26]**

From the foregoing excerpts, it can be seen that the original disclosure supports that treatment in the present invention, whether therapeutic or preventive, involves regulation (a/k/a suppression) of an autoimmune response. Support for "rodent" can be found in "mammal" (see above excerpts) and in Examples 1-6 of the present specification.

Cancellation of certain claims as provided above has resulted in items 9 and 10 of the office action outstanding being moot. Of the remaining items, only items 4 and 5-7 need to be responded to. Items 5-7 are terminal disclaimer requirements, which will be responded to as soon as allowable subject matter is indicated.

The Rejection of Claims 37-39, 48-49, 52-57, 59, 61, 62, 64 and 65 Under 35 U.S.C. §112 First Paragraph

This rejection is respectfully but firmly traversed. The present claims are drawn to treatment of an autoimmune disease in a human or rodent by suppressing an autoimmune response associated with the disease. This abnormal response is suppressed by administering to the human an amount of a bystander antigen effective to suppress this response. The claims further provide that the bystander antigen cannot be an antigen to which the T-cells of the afflicted host are sensitized, and that the bystander antigen cannot be insulin. Thus, the present claims do not encompass all bystander antigens, but only those which are pure bystanders in that the host does not have activated T-cells directed against the administered antigen.

Moreover, the present claims define treatment as suppression of an abnormal autoimmune response. Thus, the lengthy discussion in the office Action about treatment, prevention and animal models is rendered moot. The claims now require such an autoimmune response to be present.

The Examiner has concluded that only glucagon is described as a pure

bystander in the present specification. Base on this, the Examiner has rejected the claims as lacking sufficient description and enablement.

In response, we submit as follows:

The terms "autoantigen" and "bystander antigen" have been defined in the specification in a particular way. It is therefore inappropriate to cite the dictionary definitions, since a patent applicant can be his own lexicographer, and the meaning of the specification definitions controls. *Renishaw PLC v. Marposs Societa Per Azioni* 158F.3d 1243,1249, 48 USPQ 2d 1117,1121 (Fed. Cir. 1998); *accord*, *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F.3d 1190,1194, 99 USPQ 2d 1671,1675 (Fed Cir 1999). Applicants also point out that the Examiner cited a 1995 edition of a dictionary against a patent application with a filing date no later than February of 1992.

The term "bystander" has been further restricted in the present claims to exclude antigens recognized by activated T-cells. The Examiner objects, alleging in effect that the claim has been so narrowed that its subject matter is not described or enabled. However, the Examiner is under the misimpression that once a substance is called an autoantigen, it is always an autoantigen. This is not so . Applicants have constructed an experimental system in which MBP is a bystander as follows:

The Examiner's attention is directed to Example 6 in which healthy mice were immunized with PLP peptide. In that experiment, PLP is the autoantigen. Prior to the experiment, the mice did not have activated T-cells that would recognize MBP.

Accordingly, for these mice, PLP is the autoantigen, and MBP is a pure bystander antigen. Example 6 specifically calls attention to the fact that in these experiments MBP is a pure bystander as follows:

At page 50, lines 3-4, the specification states that mice were immunized with PLP peptide 140-160. This clearly establishes PLP as the autoantigen for that particular induced model of autoimmune disease EAE. See also page 50 lines 14-16.

At page 49 line 30, Example 6 provides that a group of mice were fed MBP. With respect to that group, the specification at page 50, lines 11-13 states:

> Thus, a bystander antigen, in this case mouse MBP effectively suppressed EAE when orally administered to animals induced for EAE with bovine PLP.

The foregoing constitutes direct support for use of pure bystander antigen, MBP, in a model of autoimmune disease, specifically EAE induced with the autoantigen PLP.

At p.28, lines 31-35 the specification states:

> Example 6 demonstrates tht one autoantigen can act solely as a bystander for another autoantigen. MBP was thus demonstrated to be bystander for PLP. (PLP also has the ability of suppressing MBP-induced disease and therefore PLP is a bystander for MBP.)
> This is also direct evidence that MBP can be a bystander, and nothing the Examiner has cited or said contravenes or rebuts this statement.

Thus, applicants have defined a functional genus for the invention, namely the suppression of autoimmune response by buccal or nasal administration of a pure bystander antigen. As one species of this invention, the inventors have provided the use of the bystander antigen MBP to suppress EAE induced with the autoantigen PLP. In this experiment, MBP is a bystander antigen, regardless of what dictionary definitions or literature descriptions of animal models state. Normally, MBP is considered an

autoantigen either because it is used to induce EAE or because patients with multiple sclerosis have activated T-cells recognizing it. However, neither is the case in the experiment of Example 6.

As another species of this invention, the inventors have exemplified the use of glucagon orally to suppress the inflammation termed insulitis in NOD mice which serve as a model for insulin-dependent diabetes mellitus. Insulitis is an inflammation of the pancreas. Suppression of insulitis is direct evidence of suppression of an immune response mounted by the host, the NOD mouse, against its own pancreas, i.e. an autoimmune response. Glucagon is a pure bystander because, as explained by the present specification at page 19, lines 18-23 is a pure bystander, i.e. it is present in cells of the pancreas not targeted by autoimmune response. See Example 5 at pages 48, lines 8-27; p.19 at lines 15-22. This is another species of the present invention that has been specifically exemplified in the present specification.

In addition, in Example 3, at page 45 line 9-page 46 line 18, portions of autoantigens which have been demonstrated not to participate in the autoimmune response were used as pure bystander antigens and were successful in conferring tolerance on the treated mice.

Thus, contrary to the Examiner's belief, an "autoantigen" is not a term cast in stone but it depends on the experimental context. The foregoing experiments thus provide competent evidence to confirm the general applicability of the present invention.

Finally, Example 2, which investigates the mechanism of bystander suppression

makes it even clearer that bystander suppression is a general immune phenomenon independent of the particular autoimmune disease and independent of the antigen used. As Example 2 shows (p.36, line 28-p.45) OVA, an antigen which is clearly not involved in EAE (and is therefore a pure bystander in the experimental context of Example 2), elicits bystander suppression in mice fed OVA but immunized with MBP. See Table 3, discussion at p.42-43 and Fig. 6A. This confirms the generality of bystander suppression: Modulator cells elicited by oral tolerization to one antigen can suppress cells of a different antigen when the tolerization antigen is present (p.44, lines 11-13). This experiment confirms that the antigen used (fed) to tolerize need not have any involvement in the autoimmune response and need not be tissue-specific, although tissue specificity is preferred. This experiment also confirms that suppression is mediated by nonspecific immunosuppressive cytokines (such as TGF-β), which further undermines the Examiner's allegation that the invention has not been described or enabled. If suppression is mediated by a substance that is antigen and disease-independent, then this is evidence that the invention has general applicability across the entire scope of the present claims.

The citation of Cohen et, al Autoimmune Disease Models does not contradict the present inventors. Therein, the authors describe induced models of autoimmune disease in which collagen is used to induce a model for rheumatoid arthritis and MBP is used to induce a model for multiple sclerosis. In that experimental context both collagen and MBP are autoantigens, but this fact has no applicability to the present

invention and its use of the PLP-induced model of EAE.

In view for the foregoing, it has been established that at least 2 working embodiments have been presented for different autoimmune disease models using different pure bystander antigens. Additionally, the generality of the presently claimed functional genus has been supported not only by the working examples, but by the broad statements in the present specification. Lastly, substantial support is lent to the present invention by Example 2 which demostrates the general nature of bystander suppression and its applicability regardless of the disease involved or the antigen administered. As a result, the Examiner should not dispute the compliance of the present claims with section 112 first paragraph description requirement.

Turning now to the Examiner's remarks about enablement, the same are moot in view of the amendments to the claims. The specification has amply enabled a treatment for autoimmune diseases and its models involving suppression of autoimmune response. This is reflected in all of the Examples and in the general description throughout the specification and cannot be disputed. There is thus no "timing" issue of the bystander antigen administration. Bystander, administration would be beneficial in terms of reducing autoimmune response whether it is undertaken prior or after clinical manifestation of the disease **as long as there is ongoing autoimmune response**. The present claims imply that autoimmune response is going on by virtue of their

language.

Citation of Mueller is not relevant to the present invention. Mueller has nothing to do with bystander suppression but only with anergy. As applicants pointed out in the prior response, anergy requires administration of exactly the same antigen to which the T-cells are sensitized. For this reason, anergy is not a preferred method for attacking autoimmune response. For anergy to be successful, the precise specificity of the activated T-cells needs to be known, which as the present specification states, is seldom the case. In the Office Action, the Examiner quotes a passage of Mueller in which anergy is explicitly mentioned. This supports the applicants' position that Mueller pertains to anergy, a totally different approach to tolerance induction operating on a totally different principle.

In contrast, as the present inventors have demonstrated, in the Examples of the present specification, that bystander suppression proceeds by the secretion of suppressive cuytokines which do not depend on precise (or any) identification of the determinant which the activated T-cells which mediate the disease recognize. The Examiner's persistence in citing Mueller is evidence that the Examiner does not appreciate the generality of bystander suppression. A personal interview with the participation of one of the inventors is suggested.

The Examiner's remarks as pertaining to Mueller are not applicable to the present invention. Applicants agree with the remarks of Mueller with respect to anergy as a potential mode for combating autoimmune disease. However, they do not apply to

bystander suppression.

Lastly, even though the Examiner states that she still questions the applicability of the animal model, in light of the foregoing discussion, such objection should be withdrawn. The animal models amply show bystander suppression as claimed. Moreover, the Examiner's lengthy discussion about the reliability of models is moot in view of the amendments to the claims.

The objection as to the predictability of whether a person is going to develop Type I diabetes is also moot in view of the claims being amended to require suppression of autoimmune response. In fact, the specification does provide guidance for predicting which persons will develop diabetes, and this group is ascertainable. See p.18, lines 3-14. The Examiner does not provide contrary evidence nor her own affidavit.

Amounts and Guidance

The ordinarily skilled person would also receive guidance from the present specification as to amounts to use. The fact that bystander suppression in antigen-independent makes the teachings of the present specification applicable to bystander antigens even if cost in terms of antigens that sometimes are not bystander antigens.

The present specification discloses many amounts, dosages and frequency of administration, as follows. See for example p.24, lines 3-9 and 25-29; p.25, lines 3-5; and p.23, lines 4-9; P.17, lines 4-34 (especially lines 22-31) and p.18, lines 1-2. The Examiner has not provided evidence that the given information is inadequate.

Moreover, in light of the present discussion as to the meaning of autoantigen and bystander, the disclosure of all amounts is pertinent to the present claims. Moreover, the guidance of the specification does not become inadequate just because the claim has been narrowed.

SUMMARY

The present claim 37 is drawn to a genus of a method for suppressing autoimmune response associated with autoimmune decrease comprising administering to a host by mouth or nasal route an antigen to which (activated) T-cells of the host are not sensitized. The species claims include administration of glucagon to suppress an immune response associated with IDDM. This embodiment is exemplified in Example 5.

There is also another species of the invention exemplified in Example 6: therein health mice have been immunized with a PLP peptide ("autoantigen") to induce EAE, a model for multiple sclerosis. These mice therefore have activated T-cells that recognize the PLP peptide. One subgroup of mice was treated orally with MBP, which in the context of this experiment is a pure bystander antigen. The teaching of this experiment is that suppression of autoimmune response with a pure bystander antigen is not confined to one antigen nor to one disease or host.

The generality of the foregoing is further demonstrated in Example 3 which shows how that peptides which are incapable of inducing disease are nevertheless capable fo eliciting suppression of autoimmune response. This is yet another working example

with another species of the invention.

Finally, Example 2 makes clear that the mechanism of bystander suppression is of general applicability: bystander suppression is mediated by suppressor T-cells which secrete suppressive cytokines. The suppressor T-cells are drawn to the locus of autoimmunity because the bystander antigen was chosen to be expressed at such locus. However, in all other respects, bystander suppression is antigen-independent. Thus, the present application provides a representative number of species.

Additionally, a person of ordinary skill would readily recognize whether a person's T-cells are sensitized to an antigen. Hence bystander antigens are readily ascertainable in light of the present specification, and the amounts can be ascertained by reference to general teachings and by extrapolation of particular teachings. They are preferably specific to the tissue under attack, and are not recognized by the patient's T-cells.

In view of the foregoing, reconsideration of this application is respectfully requested and allowance of the present claims respectfully solicited.

Respectfully submitted,

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